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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,696	10/28/2005	Shuji Ozaki	14875-141US1 C1-A0220P-US	1270

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
11/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,696	OZAKI ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,13-25,27-38 and 40-45* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 13-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,25,27-38 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/12/08, 5/21/08, 6/11/08, 8/29/08, 9/13/08.

DETAILED ACTION

1. Applicant's arguments filed August 5, 2008 have been entered.

2. No claims have been amended, canceled or added.

3. Claims 1-6 and 13-23 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 16, 2006.

4. Claims 24, 25, 27-38, and 40-45 are under examination.

5. The following office action contains NEW GROUNDS of Rejection.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on February 12, 2008, May 21, 2008, June 11, 2008, August 29, 2008, and September 13, 2008 were filed after the mailing date of the first action on the merits on December 21, 2006. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Rejections Withdrawn

7. The rejection of claims 24, 25, 27-38, and 40-45 under 35 U.S.C. 103(a) as being unpatentable over Oka, et al. in view of Reff and Heard is withdrawn in view of applicant's arguments.

NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 24, 25, 27-38, and 40-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for producing an HLA class I antigen recognizing minibody that has increased cytotoxicity. The specification describes a 2D7 antibody that binds to HLA class I antigen and has increased cytotoxicity in minibody form. There is insufficient written description as to the genus of antibodies that would increase cytotoxicity in minibody form.

Genestier, et al. (Blood, 1997. Vol. 90, pages 3629-3639, as cited on applicant's IDS filed 6/30/06) teach monoclonal antibodies that bind to HLA class I. Genestier, et al. teach MoAb90 and YTH862 induce apoptotic cell death of activated T lymphocytes, but antibodies B9.12.1, W6/32, and TP25.99 had little or no apoptotic effect (see table 2). Genestier, et al. suggest that α1 domain induced apoptosis does not require cross-linking and excludes a possible Fc-receptor mediated antibody-dependent-cytotoxicity mechanism (see discussion page 3636). Thus, the broad genus of HLA class I antibodies would not be cytotoxic.

Regarding a species of antibody the court found the written disclosure requirement was not met where the claims at issue covered a broad "genus of recombinant plasmids that contain coding sequences for DNA polymerase . . . from any bacterial source, [but] the narrow specifications of the [relevant patents] only disclose[d] the . . . gene coding sequence from one bacterial source . . . ." (Carnegie Mellon Univ. v. Hoffman-LaRoche Inc., 541 F.3d 1115, 1125 (Fed. Cir. 2008)). Further in In re Alonzo it was found that "the specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient. The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language – 'a monoclonal antibody idiotypic to the neurofibrosarcoma of said human.' This sparse description of

antibody structure in the claim stands in stark contrast to the detailed method of making the antibodies found in the specification" (see In re Kenneth Alonso, US Court of Appeals for the Federal Circuit, online opinion, October 30, 2008).

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*.

Applicant's 2D7 antibody is not representative of the genus given the data of Genestier, et al. which support not all HLA class I antibodies have cytotoxic activity and the instant disclosure does not characterize or identify the epitope or structure connected with the cytotoxic activity.

Therefore, only the 2D7 antibody meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.).

Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 24, 25, 27-29, 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Woodle, et al. (Transplantation, 1997. Vol. 64, pages 140-146, as cited on applicant's IDS filed 6/30/06).

The claims recite a method for producing an HLA class I antigen-recognizing minibody, the method comprising: (a) identifying a whole antibody that recognizes an HLA class I antigen; (b) producing a minibody version of the antibody of (a); and (c) assaying a cytotoxic activity of the minibody, further comprising: (d) determining whether the minibody has an increased cytotoxic activity compared to the antibody of (a), wherein the HLA class I antigen is an HLA-A antigen, wherein the antibody of (a) is an IgG, wherein the minibody comprises a Fab, a Fab', a F(ab')2, a Fv, an scFv, or a diabody, wherein the cytotoxic activity is a cell death-inducing activity.

Woodle, et al. teach an anti-HLA-A antibody 5H7 which is an IgG2a monoclonal antibody. Woodle, et al. teach digestion of the 5H7 antibody with pepsin or papain to produce F(ab')2 or Fab fragments of the antibody. Woodle, et al. teach measurement of cytotoxic activity for both the full length 5H7 antibody and the F(ab')2 and Fab antibody fragments (see figure 6) and the antibodies inhibit the growth of tumor cells (i.e., growth-suppressing activity). Since the claims do not define the specific HLA-A antibody or the effect of producing the minibody, all the limitations have been met.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 24, 25, 27-38, and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle, et al. (Transplantation, 1997. Vol. 64, pages 140-146, as cited on applicant's IDS filed 6/30/06) in view of Ghetie, et al. (US PAT 6,368,596, issued April 9, 2002, as cited on applicant's IDS filed 6/30/06) as evidenced by the specification.

Claims 24, 25, 27-29, 33 and 34 have been described supra. Claims 30-32, 35-38, and 40-45 recite a method of producing a minibody, the CDRs of which are derived from the CDRs of an HLA class I antigen-recognizing whole antibody, wherein the minibody has a level of cytotoxic activity greater than that of the whole antibody, the method comprising: (a) providing a DNA encoding the minibody; (b) expressing the minibody from the DNA; (c) confirming that the expressed minibody possesses cytotoxic activity greater than that of the whole antibody, wherein the minibody comprises human framework regions, wherein the whole antibody is a human antibody, wherein the whole antibody is a non-human antibody and the minibody is humanized, wherein the HLA class I antigen is an HLA-A antigen, wherein the minibody comprises an scFv or a

diabody, wherein the cytotoxic activity is a cell death-inducing activity or a cell growth-suppressing activity.

Woodle, et al. has been described supra. Woodle, et al. teach cross-linking of 5H7 F(ab')2 restored programmed cell death (apoptosis) and antibody cross-linking is necessary for apoptosis induction. Woodle, et al. do not teach a minibody with increased cytotoxic activity. This deficiency is made up for in the teachings of Ghetie, et al.

Ghetie, et al. teach conjugates of monoclonal antibodies which do not possess an Fc region of the antibody. Ghetie, et al. teach crosslinking of mIg initiates a cascade of signals leading to apoptosis (column 1 lines 47-50). Ghetie, et al. teach antibodies which signaled weakly increased cytotoxic or growth inhibiting functions when crosslinked as multivalent molecules (columns 11 and 12). The specification defines a minibody as an antibody that lacks a portion of a whole antibody (page 5, lines 19-20).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the HLA-A antibody of Woodle, et al. and produce a minibody with increased activity in view of Ghetie, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the HLA-A antibody of Woodle, et al. and produce a minibody with increased activity in view of Ghetie, et al. because Ghetie, et al. teach Fc regions elicit undesired immune responses which reduce successful treatment of a tumor or neoplastic disease (column 3 lines 50-53). Additionally, Ghetie teaches conjugates which do not possess Fc regions are surprisingly active at signaling

cell cycle growth arrest and/or apoptosis and these conjugates are capable of wider biodistribution (column 3 line 57 to column 4 line 2). Further, Ghetie, et al. teach increased cytotoxicity and cell growth inhibition with conjugated antibodies when the monomeric forms only weakly signaled growth arrest (column 12, lines 29-45). Since Woodle, et al. teach that crosslinking is necessary to induce cell death with an antibody fragment, one of ordinary skill in the art would be motivated to use the conjugated antibody form of Ghetie, et al. with the HLA-A antibody of Woodle, et al. to increase the cell death activity of the HLA-A antibody fragment. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the HLA-A antibody of Woodle, et al. and produce a minibody with increased activity in view of Ghetie, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

November 6, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643